# Revealing Intrinsically Disordered Protein Interactions with Membrane Mimic Surfactants

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α-Synuclein (αSyn) is an intrinsically disordered protein that is implicated in Parkinson's disease. Although its physiological functions are still unknown, it has been hypothesized that it may function as a presynaptic protein due to its association with the presynaptic membrane. Recent studies have shown that αSyn can adopt different conformations that are dependent on its interaction with biomolecular aggregates such as micelles and lipid membranes. However, the exact conformation that αSyn adopts and its interaction with phospholipid environments are still unclear. In order to provide insights into αSyn structure and function we are carrying out all-atom molecular dynamics simulations of αSyn with sodium dodecyl sulfate (SDS) micelles.

The intrinsically disordered protein α-Synuclein (αSyn) is abundantly expressed in the brain [1]. It is localized at the nerve termini in close proximity to synaptic vesicles. Its native function is thought to involve vesicle maintenance and recycling, modulation of neural plasticity, endoplasmic reticulum-Golgi trafficking, and dopamine reuptake. Numerous studies connect αSyn to Parkinson's disease (PD) as it has been found to form supramolecular fibrils, which are a major component of Lewy bodies and Lewy neurites (two major hallmarks of the disease). However, it is still not clear how αSyn executes its function, and what are its toxic and key conformations for fibril formation.

In solution, monomeric αSyn has no well-defined structure but appears to be more compact than a random-coil conformation. Recently, it has also been found that native αSyn exists in cells as a helically folded tetrameter. The functionality of αSyn is expected to be associated with its interaction with membranes. When interacting with lipid vesicles or membranes, αSyn typically displays two different conformations—a helix-turn-helix structure or an extended helical structure, depending on the curvature of the binding surface. On the one hand, the composition of lipid bilayers (membranes or vesicles) is known to affect the binding strength of αSyn. On the other hand, both electrostatic and hydrophobic interactions are important in the association of αSyn with lipid bilayers, and this association can lead to changes in the physical properties of bilayers.

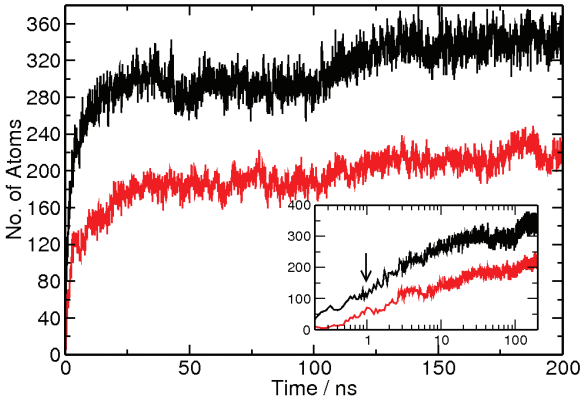


*Fig. 1. The number of SDS head group atoms (OS, S, and O) (red line) and alkyl tail atoms (black line) within 0.35 nm of the protein as a function of time for αSyn started from helix-turn-helix conformation. Inset shows the same plot with time in logarithmic scale to enlarge the details of the early interactions.*

As a lipid-membrane mimic, sodium dodecyl sulfate (SDS) has been widely used to study the role of lipid binding in modulating the conformational changes of αSyn as well as its aggregation process. A conformational interconversion between unfolded, helix-turn-helix and extended helices happens during isothermal protein-SDS titration experiments [2]. The fibrillation pathways of αSyn have been shown to differ in the presence and absence of SDS. In addition, fibrillation occurs only at low concentrations of SDS surfactant.

We are conducting extensive molecular dynamics simulations of αSyn with self-assembling and self-assembled SDS micelle systems. Our goal is to understand the details of the interactions between αSyn and SDS, and to characterize the influence of αSyn on SDS micellation.

During the simulations of the self-assembly of SDS micelles, monomeric SDS freely diffuses and interacts with the independently diffusing αSyn molecule. It binds αSyn and forms small aggregates around the whole protein. The interaction between αSyn and monomeric SDS is tracked by calculating the number of sulfate head group (OS, S, and O) atoms and alkyl chain carbon atoms within 0.35 nm of protein atoms as a function of time for all simulations (see Fig. 1).

We observed that the interaction between αSyn and SDS is not solely driven by the electrostatic interactions between the positively charged side chain of protein and the negatively charged sulfate head groups

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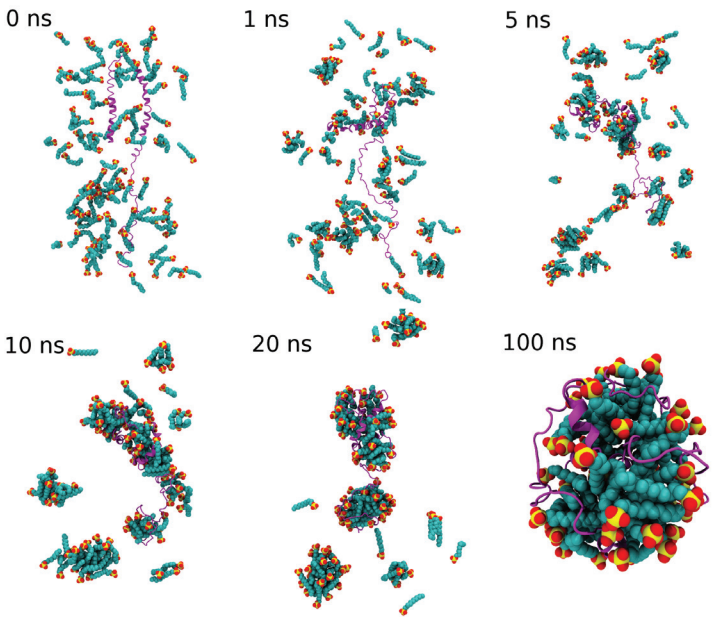


*Fig. 2. Snapshots of SDS micellation at 0, 1, 5, 10, 20, and 100 ns from the 100-folded system. Only the αSyn and SDS in the final complex are shown in the snapshot for clarity. The αSyn is in magenta cartoon presentation. The SDS molecules are in space-filling representation, while the head groups are in red and yellow and the alkyl carbon tails are in cyan. For clarity, the SDS monomers, which are not part of the final complex, are not shown.*

in SDS–there is also a significant contribution from the hydrophobic interaction between SDS tails and the apolar amino acids in αSyn. Our observation clearly confirms previous experimental results showing that the hydrophobic interaction plays an important role in SDS-protein interactions.

During micellation, we observe that SDS interacts with αSyn and forms a stable micelle-protein collapsed complex. As shown in Fig. 2, the micelle formation and the interaction with the αSyn occur simultaneously. We propose a three-stage process for initial micelle formation. First, monomeric SDS interacts non-specifically with αSyn and forms small aggregates along the protein chain. Second, the small aggregates grow by micelle fusion while the collapse of αSyn at the same time appears to promote the fusion process. Third, we observe the formation of a collapsed αSyn-SDS micelle complex.

We also consider non-rigorous quantification of αSyn secondary structure propensity at the residue level by calculating the average helix and beta-sheet percentage (Fig. 3). Residues 1 to 30 have a high helical structure propensity; residues 31 to 45 and 106 to 140 have no helical propensity, while residues 46 to 106 display intermediate helical propensity, with some interruptions. Residues 31 to 100 show a beta-sheet structure propensity. Three interruptions in helical propensity are observed in Fig. 3 for the N-terminus: residues 30 to 47, 66 to 69 and 83 to 87, all of which agree very well with the experimentally-measured regions with interruptions in helicity.

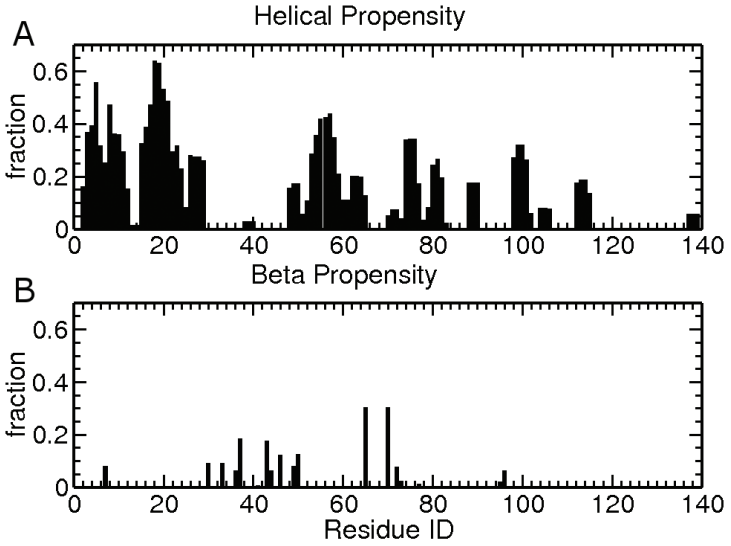


*Fig. 3. Secondary-structure propensity for each of the residues in αSyn.*

[1] George, J.M. et al., *Neuron* **15**, 361 (1995).
[2] Ferreon, A.C. et al., *Proc Natl Acad Sci Unit States Am* **106,** 5645 (2009).

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